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14. ABSTRACT

Indolent prostate cancers that pose very low risk to aged men occur frequently and may be detected at biopsy, leading to the contemporary problem of prostate cancer over-diagnosis and over-treatment. The objective of the project is to define and characterize indolent prostate cancer using genomic approaches in the clinically relevant context of a cohort meeting the entry criteria for active surveillance. During this funding period, we focused on analysis of clinical specimens suitable for RNA sequencing, and identified a finalized set of specimens taking into consideration of the age effect. We have requested a no-cost extension for an additional 12 months to allow a final analysis to be performed and reported. These progresses represent necessary interim processes that will position us for the proposed studies designed to maximize the potential impact in the context of technical advances in the field.

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Introduction

Indolent prostate cancers that pose very low risk to aged men occur frequently and may be detected at biopsy among men undergoing prostate-specific antigen (PSA) screening, leading to the contemporary problem of prostate cancer over-diagnosis and over-treatment. Since progressive acquisition of genomic alterations, both genetic and epigenetic, is a defining feature of all human cancers at different stages of disease progression, RNA and DNA alterations characteristic of indolent prostate tumors may be different from those in clinically significant prostate cancer (i.e., those requiring definitive treatment). However, due to a number of technical constraints, analysis of small volume, very low risk, indolent prostate tumors has not been systemically performed using genome-wide approaches. The primary purpose of the project is to characterize indolent prostate cancer using genomic approaches in the context of a cohort of men predicted to harbor very low-risk prostate cancer at the time of biopsy detection and thus meeting the entry criteria for active surveillance. The scope of the proposed research is: 1) to define the expression signature of indolent prostate cancer by genome-wide expression analysis comparing tissue lesions from very low risk prostate cancer versus high risk prostate cancer defined by pathological outcome measures in men meeting the entry criteria for active surveillance but opting for immediate surgical treatment; 2) to develop a refined signature using biopsy specimens from an active surveillance cohort; and 3) to differentiate indolent prostate cancer from clinically significant prostate cancer using advanced deep-sequencing technologies for both DNA copy number of methylation analysis.

Body

Findings resulting from Task 1: To define indolent human prostate cancer by genome-wide expression analysis comparing tissue lesions from RRP-confirmed very low-risk prostate cancer versus higher-risk prostate cancer (Months 1-24).

Summary: In our last annual report, we presented data justifying a modified approach to RNA analysis given the rapid advances in RNA sequencing technology that was unforeseen at the time of our original grant application. To take advantages of the new technology and on the basis of our data supporting the feasibility to apply the technology in small tumors isolated from paraffin embedded specimens, we proposed to employ RNA sequencing technology to replace the traditional microarray technology. During year 3 of the project period, we focused our efforts in accrual of suitable clinical specimens for this revised study. Following review of our progress on the tasks outlined in SOW, we communicated to CDMRP our intention to request EWOF. On October 15th, 2015, this project was officially approved for an EWOF of an additional 12 months. Therefore, this annual report will focus on a summary on patient specimen accrual. Detailed molecular analysis is still ongoing and will be reported at the time of the scheduled final report date in 2016.

During year 3 of the project period, we focused on analysis of clinical specimens suitable for RNA sequencing studies. We summarize our efforts below.

1. We identified all surgical cases from 2014 to 2015 (to minimize the age effect).
2. Working with the clinical staff members, we finalized the case selection parameters following definition of "very low-risk" prostate cancer preoperatively in biopsy specimens, as well as definition of "low-risk" and "upgraded" prostate cancer postoperatively in radical prostatectomy specimens.
3. We finalized a list of 61 surgical specimens meeting the criteria for "indolent" prostate cancer, and a list of 33 surgical specimens meeting the criteria for "upgraded" prostate cancer.
4. Molecular analysis is currently under way.

Findings resulting from Task 2: To validate a refined set of genes predictive or indicative of higher-risk disease within a PAS longitudinal cohort (Months 12-36).

Because of our revised approach and delay of Task 1, we are also experiencing a delay in executing the validation studies. This delay was expected and communicated in our last annual report. Full results related to Task 2 will be reported in the Final Report.

Findings resulting from Task 3: To define somatic DNA copy number alterations and methylation changes when higher-risk disease develops in men undergoing PAS (Months 1-36).

Summary: We have presented our progress on DNA sequencing in our year-1 progress report. Studies on DNA copy number and methylation changes are still ongoing and behind schedule. This delay was also expected and communicated in our last annual report. Full results related to Task 3 will be reported in the Final Report.

Key Research Accomplishments

1. Finalized and acquired a set of clinical specimens suitable for RNA sequencing following time-consuming efforts, and initiated molecular analysis of these specimens.

Reportable Outcomes

Manuscripts: None at this time.

Presentations: None at this time.

Grant Applications: None at this time.

Conclusion

We have concluded that our proposed studies remain feasible given that we have acquired the necessary clinical specimens, and that we have determined technical feasibility as reported in the first and second annual reports. Because of the delay in acquiring suitable clinical specimens, full study conclusions will be communicated in our Final Report.

References

N/A

Appendices

N/A

Supporting Data

N/A